II. REMARKS

Claims 2-11 and 14-16 are canceled. Claims 17-35 are new. Support for the new claims may be found throughout the application as originally filed; for example, the original claims; page 5, lines 24-34; page 6, line 1-8; page 7, lines 9-15 and 25-29; and page 8, lines 3-9 and 23-27; page 9, lines 21-24; and page 12, lines 8-11 and 21-28. No new matter is added.

Rejections under 35 U.S.C. § 102

Claims 2-5, 8, 9, 11 and 14-16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Walker et al. 1994 (Walker), Pirttila et al. 1994 (Pirttila), WO01/62801, or Naslund et al. 1994 (Naslund). Claims 2, 5, 8 and 14-16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Solomon et al. 1996 (Solomon). Claims 2, 5, 8 and 14-16 are rejected under 35 U.S.C. § 102(a) as alleged lybeing anticipated by Huse et al. 2002 (Huse). Applicants respectfully traverse the rejection as it may apply to pending claims 17-35.

Various forms of Aβ peptide occur in nature, including the N-terminal truncated Aβ11-x and the full-length Aβ1-40/1-42 (Aβ1-40/42). As Aß11-x peptides are the major species identified in the brains of patients with Alzheimer's disease (AD), it is important to specifically detect Aβ11-x without the also detecting the full length species, Aβ1-40/42, for developing effective diagnosis and treatment for AD. See specification, page 2, lines 18-24, *"Recently, it was demonstrated that BACE-1 is the major ß-secretase required for cleavage of APP at position +1 and that overexpression of BACE-1 results in an additional cleavage at the +11 site of the Aβ, generating shorter Aβ11-40 and Aβ11-42 fragments, hereinafter also referred to as the Aβ11-x peptides . . . , these shorter Aβ fragments have also been identified as major species in AD brains"*; and lines 33-35, *"the ability to monitor cellular processing of the amyloid precursor protein would be of significant value in the diagnosis, prognosis, and therapeutic supervision of Alzheimer's disease."* The antibodies of the invention are useful for this specific detection of truncated Aβ which are associated with AD, since the claimed antibodies: (a) bind to one or more epitopes on the first 5-7 amino acids of Aβ11-x, (b) bind

specifically to Aβ11-x, and (c) do not specifically bind to a full length Aβ1-40/42 peptide.

None of the cited art discloses a monoclonal antibody with all three of these characteristics. To illustrate the differences in the properties among the antibodies, Applicants submit the table below and discuss each antibody hereafter.

	Epitope of Aβ	Binds to Aβ11-x	Binds to Aβ1-40/42
Claimed antibodies	11-15/17 (first 5-7 N-terminal amino acids of Aβ11-x)	Yes	No
10D5 (Walker)	3-6 (as evidenced by Frenkel)	Unknown	Yes
4G8 (Prittila, WO01/62891 and Huse)	17-24	Unknown	Yes
266 (WO01/62801)	17-25	Unknown	Yes
6E10 (Prittila and Naslund)	4-9 (as evidenced by product description)	Unknown	Yes
AMY-33 (Solomon)	1-28	Unknown	Yes
6D/3D (Solomon)	8-17	Unknown	Yes
BAN50 (Huse)	1-10	Unknown	Yes
BNT77 (Huse)	11-16	Yes	Yes
BA27 (Huse)	Unknown	Unknown	Yes
BC05 (Huse)	Unknown	Unknown	Yes

As can be easily seen with reference to the table, all of the previously disclosed antibodies differ from the claimed antibodies in at least one way. In particular, all of the art-disclosed antibodies specifically bind to full-length Aβ1-40 and/or 1-42, in contrast to the claimed antibodies which have no specific binding to full length Aβ. Some of the antibodies of the prior art also differ from the claimed antibodies in other ways, as discussed in detail below.

Walker discloses that the monoclonal antibody 10D5 binds to Aβ1-16 and native Aβ. See page 377, right column, third paragraph, "*...we used monoclonal antibody (MAb) 10D5, a murine IgG, kappa light chain (whole IgG and/or Fab fragments) to amino acids 1-16 of Aβ.*" The antibody 10D5 is also disclosed by Frenkel et al. 1998, J. Neuroimmunology 88: 85-90 (Frenkel), submitted herein. Frenkel states that 10D5 was obtained from Dr. D. Schenk, the senior author of Walker. See Frenkel page 86, second

paragraph, *"Monoclonal antibodies, 6C6 and 10D5, raised against soluble fragment of position 1-28 of βAP, were kindly provide by Dr. D. Schenk..."* Subsequent analysis in Frenkel indicates that 10D5 has a minimal epitope of Aβ3-6 and binds to Aβ1-40. See Frenkel, page 88, Abstract, *"The peptide EFRH inhibits binding of . . . 10D5 to β-amyloid peptide in affinities identical to those obtained with the peptides corresponding to positions . . . 1-40 of [A]β-peptide. These findings confirm that the peptide EFRH which is located at positions 3-6 within β-amyloid peptide represents the sequential epitope of . . . 10D5."* Thus, 10D5, disclosed by Walker, differs from the claimed antibody in all three ways: the Aβ epitope to which it binds (3-6 vs. 11-15/17), its lack of specificity for Aβ11-x and its specificity for full length Aβ1-40.

Pirttila discloses the monoclonal antibodies 4G8 and 6E10. 4G8 is also disclosed in WO01/62801; 6E10 is also disclosed in Naslund. The properties of these antibodies are discussed below.

WO01/62801 discloses that monoclonal antibodies 266 and 4G8 bind to full-length Aβ1-40/42; see Example 15, *"Using this method, the affinity of mouse antibody 266 for both Aβ1-40 and for Aβ1-42 was found to be 4pM. The affinity of 4G8 for Aβ1-40 was 23nM and for Aβ1-42 was 24nM."* The binding epitope of 266 is identified to be Aβ17-25; see Example 16 of WO01/62801, *"the binding epitope for the mouse antibody 266 appears to be between amino acids 17 and 25 of Aβ."* Additionally, the binding epitope of 4G8 is identified as Aβ17-24 in Prittila; see page 91, right column, fourth paragraph, *"The monoclonal antibody (mAb) 4G8 was specific to an epitope present on 17-24 amino acids of the Aβ-peptide..."* Accordingly, 266 and 4G8 differ from the claimed antibody in at least two ways: the Aβ epitope to which they bind (17 to 24/25 vs. 11-15/17) and the specificity for full length Aβ1-40/42.

Naslund and Pirttila both disclose the monoclonal antibody 6E10. Subsequent analysis of this antibody indicates that the epitope of the 6E10 antibody is within Aβ4-9; see product prescription submitted herein. Naslund also discloses that 6E10 binds to full-length Aβ1-40/42; see page 8380, Figure 2B, showing an SDS/PAGE analysis of crude extract and purified monomeric Aβ1-40/42 with a molecular weight of 4 kDa which is identified by immunoblotting with 6E10. According to Naslund at page 8379, right column, first paragraph, *"[t]he indicated 4-kDa peptide (Fig. 2b) was identified as Aβ*

peptide by N-terminal microsequencing." Thus, 6E10 differs from the claimed antibody in at least two ways: the Aβ epitope to which it binds (amino acids 4-9 vs. 11-15/17) and the specific binding to full length Aβ1-40/42.

Solomon discloses the monoclonal antibodies AMY-33 and 6F/3D, both of which bind to full-length Aβ1-40. See page 452, and right column, third paragraph, *"Synthetic βA4-(1-40) was obtained from Sigma...To determine the soluble βA4 the supernatants were then incubated for another 60 min with an excess of mAb AMY-33 and/or 6F/3D...to produce immunocomplexed βA4."* Thus, AMY-33 and 6F/3D differ from the claimed antibody in at least one way: specific binding to full-length Aβ1-40.

Huse discloses the monoclonal antibodies 4G8, BAN50, BNT77, BA27, and BC05. The differences between 4G8 and the claimed antibodies are discussed above. According to Huse, BAN50 recognizes Aβ1-10 and binds to Aβ1-40/42, BNT77 recognizes Aβ11-16 and binds to both Aβ1-40/42 and Aβ11-x, BA27 binds to Aβ1-40 and BC05 binds to Aβ1-42. See page 16279, left column, fourth paragraph *"mAbs BAN50 and BNT77, directed against amino acids 1-10 and 11-16 of Aβ, respectively, were used as capturing antibodies. End-specific, horseradish peroxidase-conjugated mAbs BA27 (for Aβ40) and BC05 (for Aβ42) were then used for detection."*; and page 16280, left column, first paragraph, *"BAN50 captures primary Aβ1-40 and Aβ1-42, whereas BNT77 detects N-terminally truncated species as well as full-length peptides."* Thus, the antibodies disclosed in Huse all differ from the claimed antibody in at least one way: the specificity for full-length Aβ peptides. Additionally, at least antibody 4G8 and BAN50 recognize a different epitope than the claimed antibodies.

Clearly, none of the antibodies in the cited documents have all three properties of the claimed antibody. Therefore, Walker, Pirttila, WO/0162801, Naslund, Solomon and Huse do not anticipate the monoclonal antibody recited in the claims.

The Office Action stated, at page 5 that

> Applicant has provided no showing that the antibodies in the art have characteristics different from those specified by Applicant and do not in fact cross react with the full length of Aβ1-40/42 in the same titration or at the same concentration as those of the prior art. Since the claimed antibody is substantially identical in structure or composition and is able to bind to Aβ11-x, the antibodies disclosed by [the cited art] fairly anticipate the claimed

antibody because Applicant fails to demonstrate that the claimed antibody has a function, property or characteristics different from the antibodies disclosed by the art.

Contrary to the implication of this assertion, it is not necessary for Applicants to submit side by side data showing the claimed antibodies differ from the prior art, since the prior art teaches that the claimed antibodies have at least one characteristic which differs from the antibodies of the claims: namely, specific binding to full length Aβ1-40 and/or Aβ1-42. As can be seen in Fig. 2A, 2B and 2C of the captioned application showing data for an antibody of the claims, the claimed antibody does not bind to full length Aβ1-40, even at concentrations as high as 1000 ng/ml; yet it binds to Aβ11-x at a concentration as low as 0.1 ng/ml. The prior art teaches that all antibodies described therein specifically bind to Aβ1-40/42. The Examiner has not presented any reasoning to doubt the veracity of the statements in the art that the disclosed antibodies specifically bind to full-length Aβ1-40/42; nor any reasoning to doubt the data in the specification showing specific binding to Aβ11-x, and no specific binding to full length Aβ1-40. Thus, the claimed antibodies do, in fact, differ from the antibodies disclosed in the prior art, despite their structural similarity as antibodies.

Accordingly, the rejection is obviated. Reconsideration and withdrawal of the rejection under U.S.C. § 102 are respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 2-5, 8, 9, 11 and 14-16 are rejected to under 35 U.S.C. § 103(a) for allegedly being unpatentable over Huse in view of Walker and WO01/62801. Applicants respectfully traverse this rejection as it may be applied to the pending claims.

As discussed above, all of the antibodies disclosed in Huse lack one or more properties of the claimed antibodies. None of the art provides motivation to modify the antibodies of Huse to arrive at the claimed antibodies.

One of the antibodies disclosed in Huse, BNT77, was produced using the Aβ11-16 immunogen (including the epitope of the claims) and binds N-terminal truncated (Aβ11-x) peptides. However, in contrast to the claimed antibodies, BNT77 also binds to full-length (Aβ1-40/42) Aβ peptides. One of ordinary skill in the art, reading Huse,

would not have been motivated to produce an antibody of the claims, since it flows from Huse that an antibody which could specifically bind to N-terminal truncated Aβ peptides at one or more epitopes in the first 5-7 N-terminal amino acids would also specifically bind to full-length Aβ1-40/42 peptides. In fact, Huse teaches away from producing the claimed antibody, since it teaches that an antibody produced with the first 5 N-terminal amino acids of Aβ11-x would also necessarily bind to full-length Aβ1-40/42 peptides.

Both Walker and WO01/62801 are silent as to whether the antibodies disclosed therein specifically bind to Aβ11-x peptides. The antibodies of both Walker and WO01/62801 bind to full length Aβ1-40/42 peptides. Therefore, they do not cure the deficiency in Huse.

Accoridngly, the rejection is obviated. Reconsideration and withdrawal of the rejection under U.S.C. § 103 are respectfully requested.

Rejections under 35 U.S.C. § 112

Claims 14 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for diagnosis of Down's syndrome. Claim 16 is rejected to under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "support".

Claims 14 and 16 are canceled. Accordingly, the rejections are moot. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112 are respectfully requested.

Rejections under 35 U.S.C. §§ 102/103

Clams 2, 6, 7, 15 and 16 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by or 35 U.S.C. §103(a) as alleged being obvious over U.S. Patent No. 6,984,720 ('720 patent). Specifically, the Office Action states that *"Since the 5C4 monoclonal antibody of the* '720 patent *can block amyloid accumulation in AD patients, it indicates that 5C4 monoclonal antibody of the* '720 patent *has the same property and function as the claimed antibody..."* Applicants respectfully traverse this rejection as it may be applied to the pending claims.

The '720 patent discloses antibodies specific to a completely different molecule than Aβ11-x. The antibodies diclosed in the '720 patent are specific for human T cell

surface molecule CTLA-4. See column 4, lines 11-14, *"In particular, it relates to novel human sequence antibodies against human CTLA-4 and methods of treating human diseases and infections using these antibodies."* Nowhere in the '720 patent does it teach or suggest an antibody which binds to an Aβ peptide, let alone an antibody which binds to an Aβ11-x peptide at one or more epitopes in the first 5-7 N-terminal amino acids. The rejection seems to be based on the fact that the '720 patent refers to one of the CTLA-4 antibody producing hybridomas with the designation "5C4". According to the Office Action, "the 5C4 antibody disclosed by the '720 patent has the same name as described in the instant specification." However, this is simply untrue. While the instant specification does include "5C4" in the name of one of the hybridoma cultures disclosed therein, the full name of the hybridoma culture is disclosed as "5C4 (J&JPRD/hAβ11/2)". See specification, page 21, lines 25-29, *"…2 hybridoma cells's named 29B5 (J&JPRD/hAβ11/1) and 5C4 (J&JPRD/hAβ11/2) were successfully cloned and frozen in liquid Nitrogen."* The '720 patent does not disclose a hybridoma with this full designation. Thus, the '720 patent fails to disclose any hybridoma with even the same name as any of the hybridomas of the claimed invention.

The Office further reasons that since "the 5C4 monoconal antibody of the '720 patent can block amyloid accumulation in AD patients, it indicates that the 5C4 monclonal antibody of the '720 patent has the same property and function as the claimed antibody, which is capable of binding to Aβ11-x, and thus the binding of the '720 patent patent's 5C4 monoclonal antibody to Aβ11-x would be an inherent feature of the antibody." In order to establish inherency, the Office must provide a basis in fact or reasoning that the inherent characteristic necessarily would be present in prior art. However, the Office has failed to provide any sound reasoning or fact why all three characteristics of the claimed antibody would necessarily flow from the teachings of the '720 patent.

The Office has failed to provide any evidence or reasoning to show that all antibodies which block amyloid accumulation in Alzheimer's patients, or even all antibodies which bind to CTLA-4, also would bind to the first 5-7 amino acids of Aβ11-x. In fact, the '720 patent teaches that the mechanism by which the disclosed antibodies block amyloid deposition is through induction of autoimmune reponses to amyloid

deposits, and not through binding directly to amyloid peptides. See column 44, line 46 to column 45, line 19 *"The ability of anti-CTLA-4 antibodies to provoke and amplify autoimmune responses has been documented in a number of experimental systems . . . Therefore, it is possible to consider using anti-CTLA-4 blockade in conjunction with various self proteins in order to devise vaccination protocols to efficiently generate immune responses against these self proteins for disease treatment. . . Analogous methods as described above for the use of anti-CTLA-4 antibody can be used for induction of therapeutic autoimmune responses to treat patients having an inappropriate accumulation of other self-antigens, such as amyloid deposits, including Aβ in Alzheimer's disease..."* Thus, there is no reason to assume or conclude that an antibody which binds to CTLA-4 would also necessarily bind to one or more epitopes in the first 5-7 amino acids of Aβ11-x.

Since the antibodies of the '720 patent do not necessarily include all the characteristics of the claimed antibodies, the claims are patententable over the '720 patent. Reconsideration and withdrawal of the rejection under 35 U.S.C. §§ 102/103 are respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 2-11 and 14-16 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huse in view of Walker, WO01/602801 and further in view of '720 patent.

As discussed above, Huse fails to teach an antibody with all three claimed characteristics and in fact teaches away from the claimed antibody. None of the secondary references cure the deficiencies of Huse. As stated above, none of Walker, WO01/602801 and '720 patent disclose or suggest the specific binding to Aβ11-x at the first 5-7 N-terminal amino acids, and not specific binding to Aβ1-40/42 of the claimed antibody.

Accordingly, the rejection is obviated. Reconsideration and withdrawal of the rejection under are 35 U.S.C. § 103 respectfully requested.

III. CONCLUSION

Early consideration and prompt allowance of the claims are respectfully requested. Should the office require anything further, it is invited to contact applicants' representative at the telephone number below.

Respectfully submitted,

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